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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/786,746 | 04/18/2001 | Akihiko Sano | 0020-4828P | 5150 |

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| EXAMINER |
|---|
| BENNETT, RACHEL M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | 13 |

DATE MAILED: 07/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/786,746 | SANO ET AL. | |
| | Examiner | Art Unit | |
| | Rachel M. Bennett | 1615 | |

*-- The MAILING DATE of this communication appears on the cover she t with the correspond nce address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

The examiner acknowledges receipt of Preliminary Amendment C filed 4/30/03.

### *Specification*

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-5, 8-12, 15-18 are rejected under 35 U.S.C. 103(a) as being obvious over Fujioka et al. (US 5851547) in further view of Sanko Co. Ltd. (P 57093909 – abstract).

Fujioka discloses a drug formulation for producing sustained therapeutic efficacy, which releases at least one water-soluble drug over a prolonged period of time at a substantially constant rate wherein the drug formulation comprises (a) a non-disintegrating inner layer comprised of a biocompatible material that contains at least one uniformly dispersed water soluble drug; and (b) an outer layer comprised of a biocompatible material that surrounds the circumference of the said inner layer, is impermeable to water, and is capable of controlling the swelling of the inner layer; wherein the ratio of the axial length of the drug formulation to the cross-sectional diameter of the inner layer is one or more and wherein one or both ends of the inner layer are open so as to come into direct contact with the external environment (see abstract, claims and figures). The release rate of water-soluble drug is controlled through control of water infiltration. The outer layer material is not critical as long as it is biocompatible, is impermeable to water, and can control the swelling of the inner layer. Hydrophobic polymers are typically

used for this purpose. The non-biodegradable polymers may be exemplified by, but not limited to silicones, polyethylenes or polypropylenes. The inner layer material may be either biodegradable or non-biodegradable (see cols. 5 and 6). Any water soluble drug by be used that is not soluble nor diffusible to the outer layer. Drugs include peptides, proteins, glycoproteins, polysaccharides, nucleic acids, antibiotics, adrimycin, mitomycins, and daunorubicin (see cols. 6 and 7). The inner layer may contain a swelling agent such as sodium chloride, amino acids and glycine. The drug formulation may have a rod-shaped (see col. 7 lines 46-52). Fujioka discloses the combined quantity of drug, swelling agent, and additive present in the inner layer is not particularly specified provided that dispersion and molding are substantially possible. This quantity will vary as a function of the inner and outer layer materials. The drug content will of course vary in accordance with the type of drug, the disease under treatment and its severity. The reference does not teach polyethylene glycol as the water-soluble substance nor does the reference state some drugs are hydrophilic.

Sanko Co. Ltd. discloses antitumor composition containing lipophilic antitumor agent (e.g. carboquone, mitomycin C, daunorubicin, actinomycinD) in a liposome membrane consisting of phospholipids. The composition concentrate towards specific organs such as lung, liver, spleen, and lymphnode, by which the antitumor agent can be brought to the organ in high concentration. Therefore, achieving enhancement of the antitumor action, with a decrease of dose and reduction of side effects.

Absent unexpected results, it is the position of the examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka ('547) by using polyethylene glycol in the inner layer because Fujioka

('253) teaches polyethylene glycol may be added to the silicone elastomer in order to control the release rate of the pharmaceutical substance. Therefore, one of ordinary skill in the art would expect to achieve the desired constant release rate of the pharmaceutical using polyethylene glycol in the inner layer. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka ('547) by using lipophilic drugs taught by Sanko Co. Ltd. because of the expectation of treating tumors with an enhanced antitumor action with a decreased dose and reduction of side effects as taught by Sanko Co. Ltd. Both Fujioka ('547) and Sanko Co. Ltd. teach mitomycins and daunorubicin as effective drugs. Therefore it would have been obvious to one of ordinary skill in the art to use lipophilic drug because of the benefits listed above as taught by Sanko Co. Ltd.

3. Claims 1-6, 8-13, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujioka et al. (US 5851547) and further in view of Sanko Co. Ltd. (P 57093909 – abstract) and Fujioka et al. (US 4985253).

Fujioka discloses a drug formulation for producing sustained therapeutic efficacy, which releases at least one water-soluble drug over a prolonged period of time at a substantially constant rate wherein the drug formulation comprises (a) a non-disintegrating inner layer comprised of a biocompatible material that contains at least one uniformly dispersed water soluble drug; and (b) an outer layer comprised of a biocompatible material that surrounds the circumference of the said inner layer, is impermeable to water, and is capable of controlling the swelling of the inner layer; wherein the ratio of the axial length of the drug formulation to the cross-sectional diameter of the inner layer is one or more and wherein one or both ends of the

inner layer are open so as to come into direct contact with the external environment (see abstract, claims and figures). The reference does not teach polyethylene glycol as the water-soluble substance nor does the reference state some drugs are hydrophilic.

Sanko Co. Ltd. discloses antitumor composition containing lipophilic antitumor agent (e.g. carboquone, mitomycin C, daunorubicin, actinomycinD) in a liposome membrane consisting of phospholipids. The composition concentrate towards specific organs such as lung, liver, spleen, and lymphnode, by which the antitumor agent can be brought to the organ in high concentration. Therefore, achieving enhancement of the antitumor action, with a decrease of dose and reduction of side effects.

Fujioka discloses a sustained release composition which comprises a silicone elastomer, a pharmaceutical substance and optionally albumin. The pharmaceutical substance may be peptides, proteins, sugars proteins or polysaccharides (see abstract and col. 2). The release rate of the pharmaceutical substance from the silicone elastomer can be controlled by incorporating a mixing agent such as polyethylene glycol (see col. 3).

Absent unexpected results, it is the position of the examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka ('547) by using polyethylene glycol in the inner layer because Fujioka ('253) teaches polyethylene glycol may be added to the silicone elastomer in order to control the release rate of the pharmaceutical substance. Therefore, one of ordinary skill in the art would expect to achieve the desired constant release rate of the pharmaceutical using polyethylene glycol in the inner layer. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka ('547) by

using lipophilic drugs taught by Sanko Co. Ltd. because of the expectation of treating tumors with an enhanced antitumor action with a decreased dose and reduction of side effects as taught by Sanko Co. Ltd. Both Fujioka ('547) and Sanko Co. Ltd. teach mitomycins and daunorubicin as effective drugs. Therefore it would have been obvious to one of ordinary skill in the art to use lipophilic drug because of the benefits listed above as taught by Sanko Co. Ltd.

4. Claims 1-5, 7-12, 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujioka et al. (US 5851547) and further in view of Sanko Co. Ltd. (P 57093909 – abstract) and Remington's Pharmaceutical Sciences.

Fujioka discloses a drug formulation for producing sustained therapeutic efficacy, which releases at least one water-soluble drug over a prolonged period of time at a substantially constant rate wherein the drug formulation comprises (a) a non-disintegrating inner layer comprised of a biocompatible material that contains at least one uniformly dispersed water soluble drug; and (b) an outer layer comprised of a biocompatible material that surrounds the circumference of the said inner layer, is impermeable to water, and is capable of controlling the swelling of the inner layer; wherein the ratio of the axial length of the drug formulation to the cross-sectional diameter of the inner layer is one or more and wherein one or both ends of the inner layer are open so as to come into direct contact with the external environment (see abstract, claims and figures). The reference does not teach sodium lauryl sulfate as the water-soluble substance nor does the reference state some drugs are hydrophilic.

Sanko Co. Ltd. discloses antitumor composition containing lipophilic antitumor agent (e.g. carboquone, mitomycin C, daunorubicin, actinomycinD) in a liposome membrane consisting of phospholipids. The composition concentrate towards specific organs such as lung,

liver, spleen, and lymphnode, by which the antitumor agent can be brought to the organ in high concentration. Therefore, achieving enhancement of the antitumor action, with a decrease of dose and reduction of side effects.

Remington's Pharmaceutical Sciences discloses sodium lauryl sulfate as a surfactant. Surfactants are known in the art to increase solubility of the active agent; improve dissolution of the active agent; improved solubilization of the active agent; enhance absorption and/or bioavailability of the active agent; and improve stability, both physical and chemical, of the active agent.

Absent unexpected results, it is the position of the examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka ('547) by using sodium lauryl sulfate in the inner layer because Remington's Pharmaceutical Sciences teaches sodium lauryl sulfate as a surfactant and surfactants are known in the art to increase solubility of the active agent; improve dissolution of the active agent; improved solubilization of the active agent; enhance absorption and/or bioavailability of the active agent; and improve stability, both physical and chemical, of the active agent. Therefore, one of ordinary skill in the art would expect to achieve the desired constant release rate of the pharmaceutical using sodium lauryl sulfate in the inner layer. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka ('547) by using lipophilic drugs taught by Sanko Co. Ltd. because of the expectation of treating tumors with an enhanced antitumor action with a decreased dose and reduction of side effects as taught by Sanko Co. Ltd. Both Fujioka ('547) and Sanko Co. Ltd. teach mitomycins and daunorubicin as effective drugs.

Therefore it would have been obvious to one of ordinary skill in the art to use lipophilic drug because of the benefits listed above as taught by Sanko Co. Ltd.

***Response to Arguments***

5. Applicant's arguments with respect to claims 1-18 have been considered but are moot in view of the new ground(s) of rejection.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 309-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

R. Bennett
July 1, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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